AD_____

Award Number: DAMD17-01-1-0729

TITLE: Molecular Epidemiology of Ovarian Cancer

PRINCIPAL INVESTIGATOR: David Bowtell, Ph.D.,D.V.M.

CONTRACTING ORGANIZATION: Trescowthick Research Laboratories
Peter MacCallum Cancer Institute
East Melbourne, Victoria 8006, Australia

REPORT DATE: September 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2003	Annual (15 Aug 2002 - 14 Aug 2003)

4. TITLE AND SUBTITLE
Molecular Epidemiology of Ovarian Cancer

5. FUNDING NUMBERS
DAMD17-01-1-0729

6. AUTHOR(S)
David Bowtell, Ph.D., D.V.M.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Trescowthick Research Laboratories
Peter MacCallum Cancer Institute
East Melbourne, Victoria 8006, Australia

E-Mail: d.bowtell@pmci.unimelb.edu.au

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates: ALL DTIC reproductions will be in black and white

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

The aim of this Program is to study the association between epidemiologic risk factors, low-risk genes, and histologic and novel molecular subtypes of ovarian cancer. In December 2002, we received final approval from the Human Subject Research Review Board (HSRRB) to start recruitment at 13 of the proposed study sites. We have established a network of research nurses across the country and recruitment is now progressing well at 12 different sites. Recruitment of cases for the study began in January 2003 and control recruitment began in May 2003 and we have since recruited a total of 283 women with ovarian cancer and 155 control women. The recruitment, sample and data collection and processing systems are working well and we are continuously monitoring our performance against our targets as outlined in the reports from Core Components A (Epidemiology) and B (Biospecimens). In relation to this we also have established systems to manage data and samples from all of the different sites.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Molecular epidemiology, heterogeneity, histologic subtypes, ovarian cancer	15
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

TABLE OF CONTENTS

Cover Page 1

Standard Form 298 2

Table of Contents 3

Introduction 4

Body 4

Key Research Accomplishments 14

Reportable Outcomes 14

Conclusions 14

References 15

Appendices 15

ANNUAL REPORT

Title:	Molecular Epidemiology of Ovarian Cancer: The Australian Ovarian Cancer Study,"
Proposal No.	OC000109
Award No.	DAMD17-01-1-0729
HSRRB Log No.	A-10884.

INTRODUCTION

The aim of this Program is to study the association between epidemiologic risk factors, low-risk genes, and histologic and novel molecular subtypes of ovarian cancer, thereby addressing the heterogeneity of the disease and of susceptibility to environmental exposures. To this end, we have established a multi-center population-based resource involving collection of linked epidemiologic and clinical data and biospecimens from cases and matched controls.

BODY

Cores A and B

In December 2002, we received final approval from the Human Subject Research Review Board (HSRRB) to start recruitment at 13 of the proposed study sites. During the final months of 2002 we identified Research Nurses for each study site and set up procedures at each hospital. By January 2003 research nurses were deployed at the collecting sites (Figure 1) and we started phasing in recruitment. At the time of writing (August 2003) only 3 sites required final HSRRB approval and we expect these to be included within the next few weeks to months. Recruitment and data/sample collection is proceeding well (see Reports for Cores A, Epidemiology, and B, Biospecimens, below).

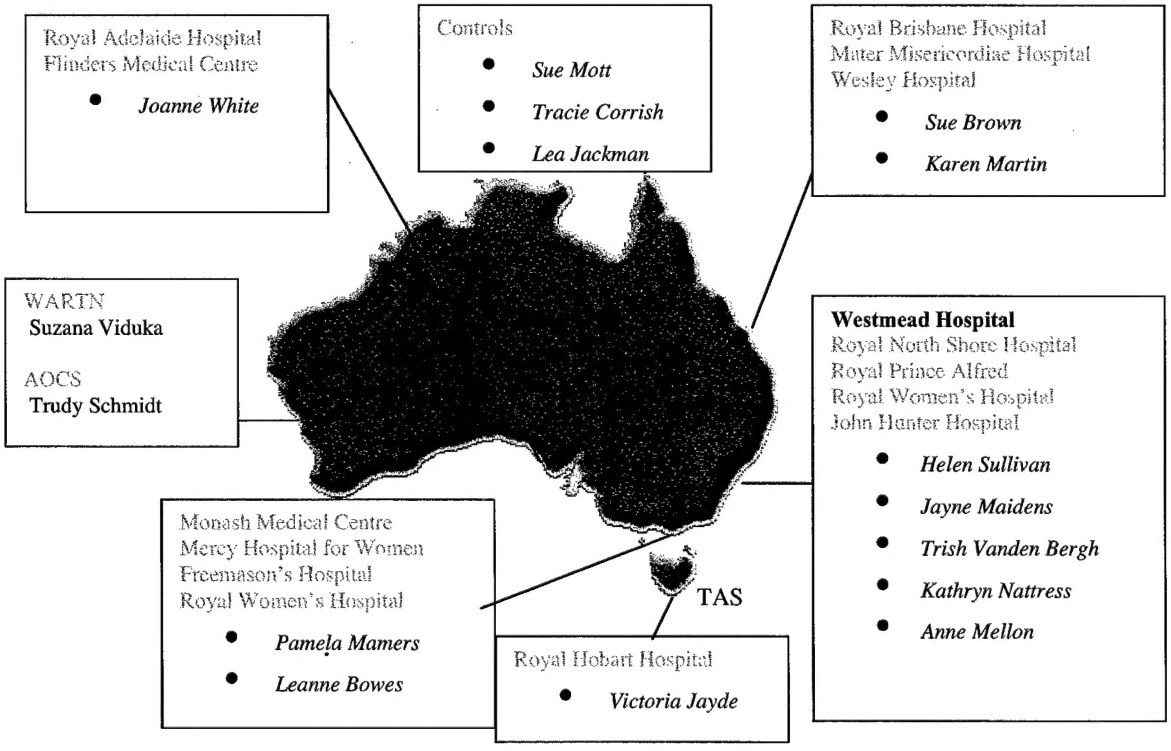

Figure 1: Australian Ovarian Cancer Study Site and RN network

Tasks Outlined in the Approved Statement of Work
Core A: Epidemiology

Task 1- Preliminary Work (Prior to start date)

(a) Data-collection instruments will be finalised and piloted based on practical experience in a previous study (Survey of Women's Health)

Completed – see 2002 Annual Report.

(b) Institutional Review Board approval will be obtained from all participating hospitals and institutions (to be prior to start date)

Mostly completed – see summary of Review Board Approvals attached.

(c) **Identification of project manager, data manager and nurse-interviewers to start on Day 1.**

The Project Manager and Data Manager have been in place for 18 months and we now have a team of part-time nurse interviewers in place at hospitals across Australia:
Queensland (2): based at QIMR and covering all hospitals
New South Wales (4): based at RHW, RPA, RNS, Westmead (plus 1 RN ready to start at John Hunter when we receive approval)
Victoria (2): based at Monash and PMCC (covering Mercy/Freemasons).
South Australia (1): based at RAH

In many cases we have employed RN's on a part time basis who are also employed for other studies at the participating sites. This had a number of advantages: the RN's were known to the clinical staff and therefore readily accepted, they had an immediate understanding of clinical processes on site, and they could be employed for just the time that was needed. Employing part time RN's at each site, rather than one full-time person to cover several sites, avoided problems associated with travelling between sites during peak hour.

Task 2- Set-up (months 1-2)

(a) Finalise details of case identification system in each of the major centres (month 1)
Case-identification systems and processes for data and sample collection have been established for all sites and the Project Manager has developed a comprehensive Procedures Manual for all study Nurses.

(b) Training of interviewers in Brisbane (month 1)
The RNs attended a two-day workshop in Brisbane for training. The Project Manager has also visited each RN and every recruitment site for additional training. Site visits to collect samples and work with RN's has been extremely useful for solving of any problems in the start up phase of the study. We are holding a follow-up training workshop in conjunction with a Breast and Ovarian Cancer Conference in Queensland in August 2003.

(c) **Development of computer data-bases (Access) for data-entry**

Recruitment "Tracking" Database
We have developed a secure internet-based database to monitor recruitment – see 2002 report.

Main Questionnaire and Dietary Questionnaire Databases
We have developed and tested the database for the main study questionnaires and have started data entry. We are in the process of setting up the dietary database and establishing procedures for quality control and data auditing.

Task 3- Recruitment of cases (n>1000). (Ongoing months 2-36)

(a) Cases will be identified by the nurse-interviewers on an ongoing basis through participating hospitals and clinics with additional checks run through the state cancer registries

(b) Treating physicians will be contacted to obtain permission to contact the case

(c) Cases will be contacted and interviewed and biological samples collected

(d) Tumor blocks and copies of pathology records will be obtained

We phased in recruitment from1 January 2003 after receiving full approval from the DoD. Recruitment is going well - see summary table below. The target figures are based on numbers of ovarian cancers registered in each state assuming that we ascertain 100% of cases in Qld and SA and 50% in Victoria and New South Wales. We were aiming for a 90% response rate and for the first 7.5 months of the year have achieved a recruitment rate of 89%. We are therefore well on track to achieve our target of 1000+ cases in three years. Return of completed questionnaires and sample collection lags slightly behind consent thus these figures do not represent final completion rates. Sample collection will be discussed further under the Biospecimen Core Report.

Case Recruitment 1 Jan 2003 – 20 August 2003

	NSW	QLD	SA	VIC	TOTAL
Target (7.5 months) (for 100% response)	**91**	**93**	**45**	**89**	**318**
Consents[1]	**74**	**101**	**52**	**56**	**283**
% of Target[1]	81%	109%	116%	63%	89%
Q returned	**49**	**82**	**38**	**31**	**200**
% of consents[2]	66%	81%	73%	55%	71%
Tissues	**40**	**39**	**23**	**38**	**140**
% of consents[3]	54%	39%	61%	68%	49%
Blood samples	**59**	**86**	**33**	**46**	**224**
% of consents[2]	80%	85%	73%	82%	79%
Urine samples	**57**	**55**	**0**	**19**	**131**
% of consents[2]	77%	54%	0%	34%	46%

Table 1. Summary collection of cases and biospecimens

[1] We are awaiting DoD approval to start recruitment at two hospitals in New South Wales and one large hospital in Victoria

[2] Questionnaire completion (and sometimes blood and urine collection) occur some weeks after recruitment and surgery thus these numbers do not represent final figures.
[3] Our target was to collect fresh tissue from 60% of cases. Early collection was slow in some centres but any procedural problems encountered initially have now been addressed.

Task 4- Recruitment of population controls (n>1000). (Ongoing months 2-36)

(a) Potential controls will be selected at random through the Commonwealth electoral roll on a weekly basis and frequency matched by age and geographic region to the distribution of cases identified the previous week
(b) Invitation letters will be sent to controls
(c) Telephone follow-up of controls
(d) Interview of controls and collection of blood and urine samples

We began control recruitment in late March 2003 and, to date, have recruited a total of 155 control women from 401 initial invitations (39%). [Note: not all women contacted have been followed up yet thus this percentage will increase] We are currently achieving an overall participation rate of >50% in a parallel study with an approximately 70% participation rate when women who are uncontactable (eg. change of address, no valid telephone number) are excluded. We are currently testing strategies to increase the participation rate including asking senior collaborators in each state to sign the approach letters and we believe this will also increase the participation rate.

Control Recruitment 1 April 2003 – 20 August 2003

	TOTAL
Target (4.5 months) (based on target case numbers)	**191**
Consents % of Target	**140** 73%
Q returned % of consents[1]	**37** 26%
Blood samples % of consents[1]	**43** 31%
Urine samples % of consents[2]	**0** 0%

[1] Questionnaires are returned and blood collected some time after consent is obtained thus these numbers do not represent final figures.
[2] We are still setting up procedures for urine collection from controls

Task 5- Data entry / checking / cleaning. (ongoing months 3-42)

(a) Data will be entered into the databases on an ongoing basis

(b) Data will be cleaned using frequency and range checks, implausible values will be cross-checked against the original questionnaires and corrected if necessary

As discussed above, we have started data entry for the main study questionnaires. The database has been designed to incorporate multiple range and logic checks to prevent errors in data entry. We are in the process of establishing procedures for auditing and to monitor data quality. The dietary database is currently being developed and data entry will commence before the end of the year.

Task 6- Data management (ongoing months 37-48)

Not started yet.

Core B- Biospecimens

Task 1- Preliminary Work (Prior to start date)

a) Institutional Review Board approval will be obtained from all participating hospitals and institutions (to be prior to start date)

Institutional Review board approval has been obtained from all participating hospitals and institutions- see summary of Review Board Approvals attached.

b) Recruitment of data manager and specimen processing staff

Project Managers and Data Managers were recruited in 2002- See 2002 Annual Report. In addition, Joy Hendley and Lisa diPrinzio (biospecimen processing staff) have been recruited to process blood, tissue and urine samples and to complete data entry for the biospecimen core.

c) Further refinement of computer data-bases (Access) for data-entry

Completed- See 2002 Annual Report.

Task 2- Set-up (months 1-2)

a) Finalise details of case ascertainment system in each of the major centres (month 1)

Completed- See 2002 Annual Report.

b) Obtain minor equipment and consumables

Completed- See 2002 Annual Report.

Task 3- Ascertainment of samples. (Ongoing months 2-36)

a) Nurse-interviewers to liase with Biorepository head, notifying of incoming shipment of samples

b) Nurse-interviewers to provide Biorepository staff with details of pathology blocks from cases to be requested. Biorepository staff to coordinate temporary block acquisition

c) **Blood and urine samples shipped overnight from national sites. Fresh frozen samples from interstate stored at centres at –80°C, shipped on dry ice at monthly intervals. Blocks from pathology clinics requested on a monthly basis.**

As discussed above, a team of part-time nurse interviewers are in place at hospitals across Australia and sample collection for the biospecimen core has been in effect since January 1 2003.

Sample collection is going well. Blood samples are shipped at room temperature on a daily basis to the Biorepository and nurse-interviewers liase directly with the Biorepository head, notifying of incoming samples. This is usually via email. Fresh frozen tissue samples and urine samples are shipped on dry ice on a monthly basis via overnight courier. Again, the nurse-interviewers notify the Biorepository head of all incoming samples.

Nurse-interviewers collect both fresh frozen and fixed tissue samples. The fixed samples shipped to PMCC on a daily basis and are processed into blocks. This means that it is no longer necessary for the biorepository staff to co-ordinate temporary access to the diagnostic blocks to obtain a slide.
In addition, an expert gynaecological pathology review panel has been established to review all cases recruited to the study. On a monthly basis, the diagnostic slides from pathology centres (where the case was first diagnosed) are called in for centralized review. This protocol has been in place for several years to facilitate ovarian cancer research in Australia and is being co-ordinated by Dr Peter Russell and the Biorepository head.

Table 1 shows the number of tissue, blood and urine samples collected since January 1 2003. We anticipate collection of 600 fresh tissue samples over the 3 years of the study (60%). Currently, tissue collection rates stand at 52%, however, there were teething problems in the earlier months of the year that prevented us from collecting frozen tissue at some sites. These issues have since been resolved and we are now collecting tissue at all sites.

Urine collection in SA has been difficult. Logistics prevent us from collecting samples at this site, however we are currently looking at ways to improve the situation.

Task 4. Sample processing and dispatch. (Ongoing months 2-36)

a) **Incoming samples of blood, urine, fresh frozen tissue and blocks to be processed as described in methods**
b) **Requested samples shipped to centres in general on a monthly basis but immediately available if needed**
c) **Sample backup to QIMR sent as batches on a monthly basis**
d) **Periodic quality control procedures to validate sample integrity**

Joy Hendley and Lisa DiPrinzio and are responsible for all biospecimen sample processing. Incoming blood, urine and tissue (frozen and fixed/blocks) samples are processed according to the AOCS protocols. A backup sample is stored separately (liquid nitrogen and -80°C) and sent via overnight courier to QIMR on a monthly basis.

We have established quality control protocols and the biorepository staff are responsible for their implementation.

Task 5. Data entry / checking / cleaning. (ongoing months 3-42)

a) Data will be entered into the databases on an ongoing basis
b) Provide data for analysis as required

Biorepository staff are responsible for entering information regarding sample collection (type of sample, date collected, date processed) and processing (fractions processed, amount processed, storage location) onto the biospecimen database.
The Data Manager, Sian Fereday, is responsible for generating monthly statistics for the management group meetings. These reports describe primary site, histology subtype and stage of the biospecimens collected.
Adhoc data requests are furnished as required.

Project 1: Molecular Subtype Analysis of Ovarian Cancer

Task 1. Initial DNA microarray analysis with ~300 archival fresh frozen samples (months 1-12)

Utilising retrospectively collected specimens of Ovarian Cancer (OvCa) a database of gene expression information has been created. The data were generated using custom printed cDNA microarray slides from The Peter MacCallum Cancer Centre Microarray Facility. These arrays contain approximately 10,500 genetic elements and have been used to profile differences in gene expression between various clinically important classes of OvCa. Over 100 samples have been profiled to date and the data analysed to investigate three major questions: correlation of expression profile with outcome, classification of LMP tumours, and classification of Krukenberg tumours.
Outcome: Genes with robustly different patterns of expression between patients with short or long survival times may be important targets for novel diagnostic or therapeutic tools. To explore this potential, analysis of array data generated from patients following standard treatment regimes was conducted. Groups of molecular profiles from patients with survival times <12 months, 12-24 months and >24 months were created. Pattern recognition algorithms were used to identify genes from the 10,500 available, whose expression correlated significantly with the survival phenotype. From this analysis a prediction model was created which was able to correctly assign patients to one of either three survival categories with approximately 80-90% accuracy. In addition, a linear formula was generated, which was capable of predicting survival time as a continuous variable from gene expression data. Importantly genes identified by the algorithms used in this study included several genes of known importance in OvCa prognosis, including TYROBP, CXCL9, CCL8 and MT1G as well as several other genes not previously shown to correlate with patient outcome. Kaplan Meier analysis of the predictions made from this analysis revealed a highly statistically significant difference between survival classes.

Further investigation and validation of these findings is planned using additional specimens from Westmead hospital. Array analysis of the archival samples has paused at present as we await the outcome of an application to the OCRP (DoD) for additional funding to continue the analysis using commercial arrays. Although we obtain high quality data from our in house arrays, there are compelling reasons to consider changing platforms now that the cost of more complex

commercial arrays has fallen.

LMP tumours: LMP tumours are an unusual class of ovarian tumours that display a relatively indolent pattern of disease, despite frequently having mutations in the ras-MAPK pathway. We have investigated expression patterns of serous and mucinous LPM tumours and have compared these patterns with their malignant counterparts. In addition, we are comparing expression patterns of LMP tumours for which we have determined their k-ras and BRAF mutation status. Preliminary data analysis indicates that LMP and malignant tumours have strikingly different expression profiles and that mutation status is overshadowed by histological subtype of the tumour. Further analysis therefore requires additional samples of known mutation status within specific histological subtypes.

Krukenberg tumours: Krukenberg tumours are gastric tumours that metastasize to the ovary but other sites, including pancreas, breast and colon are common sites of origin for Krukenberg-like tumours. Whilst patients with these tumours may be recognized at surgery or upon pathological assessment, the clinico-pathological picture is often uncertain or such patients may simply go unnoticed. Treatment of such cases with a platinum-based regimen is usually ineffective. Our findings indicate that expression profiling allows the rapid identification of unrecognized metastases to the ovary and may be of use in the clinical management of the disease. By comparing ovarian cancer expression patterns with those of a large number of other tumour types, we find a significant subset of ovarian cancer cases whose expression profiles are indicative of a non-ovarian site of origin. We believe that these studies will the generation of a diagnostic assay that can classify atypical or uncertain ovarian tumours.

Task 2 **Progressively switich to microarray analysis of prospectively collected samples (months 12-42)**

This task will commence as samples accrue and once the issue of use of a commercial platform has been resolved.

Task 3 **Ongoing statistical analysis of expression results (months 3-42)**

See Task 1 above.

Task 4 **Full statistical analysis of expression data and preparation of manuscripts (months 42-48)**

Project 2: Determinants of Epithelial Ovarian Cancer- by histologic subtype and tumor behaviour

This project will not formally commence until epidemiologic data collection is complete and it will run through the 4th year of the program. During Year 4 analysis of the specific hypotheses will proceed in parallel under the guidance of the PI and Co-investigators.

Project 3: Low-risk genes for epithelial ovarian cancer

Task 1 **To establish the 16 single nucleotide polymorphism (SNP) genotyping assays, including identification of genotyping controls (months 1-18)**

Task 2 **To genotype the cases from the Survey of Women's Health Study and controls from the Australian Breast Cancer Family Study for 16 SNPS (months 6-24)**

Genotyping has been completed for ~550 ovarian cancer cases and 300 healthy controls for 11 SNPs as indicated in the table below. Four SNPs have been excluded from genotyping because of their low frequency (0-0.5%) detected in a sample of 90-125 Australian controls [published frequencies: 4% for *HSD17B1*:A-27C (Peltoketo et al, 1994); 2.4% for *RAD50*:Arg884His (http://greengenes/llnl.gov/dpublic/ secure/reseq) and 2% for *RAD52*:Ser347Ter (Han et al, 2002)].

Gene	Polymorphism	Status
Androgen Receptor (*AR*)	CAG_n	Spurdle et al., 2002
Progesterone Receptor (*PR*)	C44T	Not Commenced
Progesterone Receptor (*PR*)	G331A	Completed
Aromatase (*CYP19*)	C>T 3'UTR	Completed
5alpha-reductase (*SRD5A2*)	Val89Leu	Completed
17βhydroxysteroid dehydrogenase (*HSD17B1*)	A-27C	Excluded
17βhydroxysteroid dehydrogenase (*HSD17B1*)	Ala238Val	Completed
17βhydroxysteroid dehydrogenase (*HSD17B1*)	Ser313Gly	Completed
17βhydroxysteroid dehydrogenase (*HSD17B4*)	Trp511Arg	Completed
BRCA2	Asn372His	Auranen et al., 2003
X-ray cross complementation (*XRCC2*)	Arg188His	Completed
X-ray cross complementation (*XRCC3*)	Thr241Met	Completed
X-ray cross complementation (*XRCC3*)	CA_n	Not Commenced
RAD50	Arg884His	Excluded
RAD52	Ser347Ter	Excluded
RAD52	Tyr418Ter	Completed

Analysis of the ***RAD52*** Y415Ter, ***XRCC2*** R188H G>A and ***XRCC3*** T241M C>T polymorphisms revealed no difference in genotype distribution between cases and controls. There was no increased risk of cancer associated with heterozygous genotype of *RAD52* Y415Ter (OR 0.55; 95% CI 0.24-1.24); *XRCC2* GA/AA genotype (OR 0.77; 95% CI 0.51-1.14), or with the *XRCC3* CT or TT genotypes (OR 0.80; 95% CI 0.59-1.09 and OR 0.92; 95% CI 0.58-1.44, respectively). There was also no indication that genotype frequency differed across ovarian cancer subgroups defined by tumour characteristics, including histology. P53 positive tumours seemed to be over-represented in carriers of the *RAD52* truncation polymorphism (100% of 7 carriers but only 64% of 142 non-carriers were p53 positive). Although the rarity of the variant genotype frequency provided little power to detect modest risks in cancer for the *RAD52, XRCC2* and *XRCC3* variants, the data suggest that none of these variants play a major role in predisposition to ovarian cancer risk at the population level.

In contrast, in collaboration with Drs Easton et al in Cambridge, we have found an association between the Asn372His genotype of ***BRCA2*** and ovarian cancer risk (Auranen et al., 2003). We genotyped a total sample of 1121 ovarian cancer cases and 2643 controls. There was no

difference in genotype frequency between control groups from the two Australian and British studies (P=0.9). The *HH* genotype was associated with an increased risk of ovarian cancer in both studies, and the risk estimate for the pooled studies was 1.36 (95% CI 1.04-1.77, P=0.03). There was also a suggestion that this risk may be greater for ovarian cancers of the serous subtype for both studies, with an OR (95% CI) of 1.66 (1.17-2.54) for the two studies combined (P=0.005). The *BRCA2* 372 *HH* genotype appears to be associated with an increased risk of ovarian cancer of a similar magnitude to that reported for breast cancer.

There was no evidence for a relationship between the variant allele and ovarian cancer risk for ***PR, CYP19*** or ***HSD17B1*** [age adjusted OR (95%CI): *PR* AG/AA genotype 0.8 (0.5-1.3), *CYP19* 3'UTR heterozygous CT genotype 0.86 (0.60-1.24), *CYP19* 3'UTR homozygous TT genotype 0.70 (0.47-1.07); V allele of *HSD17B1* A238V 1.38 (0.35-5.49); heterozygous genotype of *HSD17B1* S313G 1.22 (0.87-1.72), homozygous GG genotype of *HSD17B1* S313G 0.98 (0.65-1.47)]. These odds ratios remained largely unchanged when tumours of low malignant potential (LMP) were excluded from the analysis.

In contrast we found that there was a trend for increased ovarian cancer risk associated with the L allele of the ***SRD5A2*** V89L polymorphism (age adj OR=1.30; 95% CI=1.03-1.62; p_{trend}=0.03) which was also apparent among the invasive tumours only (OR=1.25; 95% CI=0.98-1.59; p_{trend}=0.08). A significant trend was observed for reduced ovarian cancer risk associated with the R allele of the ***HSD17B4*** W511R polymorphism (age adj OR=0.68; 95% CI=0.47-0.97; p_{trend}=0.04); the trend remained similar for the invasive tumours (age adj OR=0.75; 95% CI=0.51-1.09; p_{trend}=0.14). Genotype frequency differences across ovarian cancer subgroups defined by tumour characteristics (including histology) are being explored.

Tasks 3, 4, 5 and 6 listed below cover Years 3 and 4 and do not apply to this annual report.

Task 3	**To genotype the cases and controls from the Australian Ovarian Cancer Study for 16 SNPs (months 25-42)**
Task 4	**To perform genotyping for 2 short tandem repeat (STR) polymorphisms on both case-control studies (months 36-42)**
Task 5	**Statistical analysis of the genotyping results from the Survey of Women's Health Study and controls from the Australian Breast Cancer Family Study (months 24-36)**
Task 6	**Full statistical analysis of the genotyping results (months 40-48) and preparation of manuscripts**

PUBLICATIONS

Auranen, A., Spurdle, A.B., Chen, X., Lipscombe, J., Purdie, D.M., Hopper, J.L., Green, A., Healey, C.S., Redman, K., Dunning, A. M., Pharoah, P. D., Easton, D., Ponder, B.A.J., Chenevix-Trench, G., and Novik, K.L. BRCA2 Asn372His polymorphism and epithelial ovarian cancer risk. *International Journal of Cancer* 103:427-30 (2003)

KEY RESEARCH ACCOMPLISHMENTS

Cores A and B

We have established a network of research nurses across the country and recruitment is now progressing well at 12 different sites (See Reports for Core A Epidemiology and Core B Biospecimens). In relation to this we also have established systems to manage data and samples from all of the different sites.

Project 1

Gene expression markers of potential prognostic significance have been identified and these need to validated on additional datasets. We have developed a classification tool for Krukenberg and Krukenberg-like tumours, which is likely to be of considerable value for determining the origin of atypical ovarian tumours, especially mucinous ovarian tumours.

Project 2

This project will not formally commence until epidemiologic data collection is complete and it will run through the 4th year of the program.

Project 3

The novel finding to date from the samples from the Survey of Women's Health is the suggestion from preliminary analyses that polymorphisms in ***SRD5A2*** and ***HSD17B4*** may play a role in ovarian cancer susceptibility. This will need to be confirmed in the AOCS samples when they have been collected, but in the meantime we will determine the haplotypes at these two loci in order to find the haplotypes (and SNPs) most strongly associated with risk.

REPORTABLE OUTCOMES

N/A

CONCLUSIONS

Cores A and B

Recruitment of cases for the study began in January 2003 and control recruitment began in May 2003. We have since recruited a total of 283 women with ovarian cancer and 155 control women. The recruitment, sample and data collection and processing systems are working well and we are continuously monitoring our performance against our targets as outlined in the reports from Core Components A (Epidemiology) and B (Biospecimens).

Project 1

The array analysis has been in progress throughout 2003. Further discovery of marker genes using archival samples and their validation will develop rapidly once array analysis recommences using more complex arrays. Array analysis will also commence with prospectively collected samples, thereby creating a database of 100's of well-defined ovarian samples.

Project 2

This project will not formally commence until epidemiologic data collection is complete and it will run through the 4th year of the program.

Project 3

Of the eleven polymorphisms nominated for analysis in this project, there is preliminary evidence from the SWH that three of them (in *BRCA2, SRD5A2* and *HSD17B4*) are associated with ovarian cancer risk. Further analyses in the AOCS samples will provide independent testing of these SNPs in ovarian cancer risk, and if confirmed provide more power to look for associations with subtypes of ovarian cancer, and to start to look for gene-gene and gene-environment interactions

REFERENCES

N/A

APPENDICES

N/A